Rational hormonal management of the menopause

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Introduction

The menopause is not a disease, but the associated hormonal changes are responsible for compromising the quality of life of many women and for contributing in some women to the pathogenesis of conditions such as osteoporosis and cardiovascular disease (CVD). Central to the management of the menopause is an appreciation of the variability in the hormonal biology between individuals and, within each individual, the organ-specific synthesis of estrogens and androgens. This change in the hormonal milieu is compounded by age-related alterations in some tissues that in a minority of women may be compromised by exogenous hormone therapy. Thus, the health of the individual and the amount and timing of hormone therapy will in large measure determine its efficacy and safety. Prior to prescribing hormone therapy each woman should be classified according to her chronological age and presenting health status. Categories include:

1. healthy, normal,
2. healthy with risk factors,
3. healthy with latent disease,
4. menopausal with overt disease.

The relevance of risk factors and the biomarkers of latent disease should be judged according to their relationship to either hormonal deficiencies or to a specific underlying disease. For example, estrogen therapy lowers the postmenopausal increase in low-density lipoprotein cholesterol and may stabilize the progression of atherosclerosis [1], but it is not appropriate for the treatment of women with dyslipidaemia and overt coronary artery disease (CAD). These women require disease-specific treatment, e.g. statins.

The above should be placed in the context of the health care needs of women (*Figure 1*) and whether hormone therapy can optimize their quality of life and reduce the prevalence and morbidity of certain diseases (*Figure 2*).

The biology of estrogen synthesis and metabolism

The non-pregnant human female synthesizes two biologically active estrogens, estradiol and estrone, and much larger quantities of a biologically inert estrogen, estrone sulfate [2, 3]. Premenopausally, the source of the estrogen is primarily the ovary, and postmenopausally the periphery: the adrenal gland, adipose tissue and muscle. The synthesis and metabolism of estrogen are governed by various enzymes (sulfatase, aromatase, 17β-dehydrogenase), the activity of which is determined and controlled by specific genes (CYP 17: CYP 19; CYP 1-A-1; CYP 1-B-1). Target organs such as the breast, brain, bone and coronary artery also synthesize estrogen; the local concentration is greater than that measured in the peripheral blood [3]. Tissue estrogen sensitivity is dependent on free estradiol binding to an estrogen receptor (ER), and the interaction between the estrogen response element and ER co-activators and co-repressors [3]. Transcription resulting in the functional response of the organ may occur through this genomic mechanism, the cell membrane or an estrogen-independent second messenger system. Additional variables influencing the estrogen response of a target organ include: the distribution of ERα and ERβ (ERβ down-regulates ERα [4]); the co-localization of the androgen receptor and its modulation of ER activity (testosterone upregulates ERβ in breast tissue [5]), the hepatic synthesis of sex hormone binding globulin (SHBG) and hence the bioavailability of both endogenous and prescribed free estrogen; the isoforms of receptors and enzymes that can result in excess local estrogen synthesis and/or response to estrogen therapy [6, 7].

The clinical message

1. All naturally menopausal women are estrogen- and androgen-deficient relevant to their premenopausal cohorts. They are not estrogen-depleted.
2. The amount of estrogen synthesized (and the functional needs of estrogen-responsive organs) varies between individuals and within individuals.
3. The liver is an important modulator of estrogen synthesis and metabolism and, depending on the route of estrogen therapy, alters the type and bioavailability of estrogen and the ratio of estrogen metabolites. Some are potentially anti-carcinogenic (2-hydroxyestrone and 2-hydroxyestradiol, and 2-methoxyestradiol) and others pro-carcinogenic (16α-hydroxyestradiol, 4-hydroxyestradiol).

Clinical application: principles

1. Estrogen therapy is additive to endogenous estrogen synthesis. Since the latter increases with age (via peripheral aromatization of androgens), the dose of

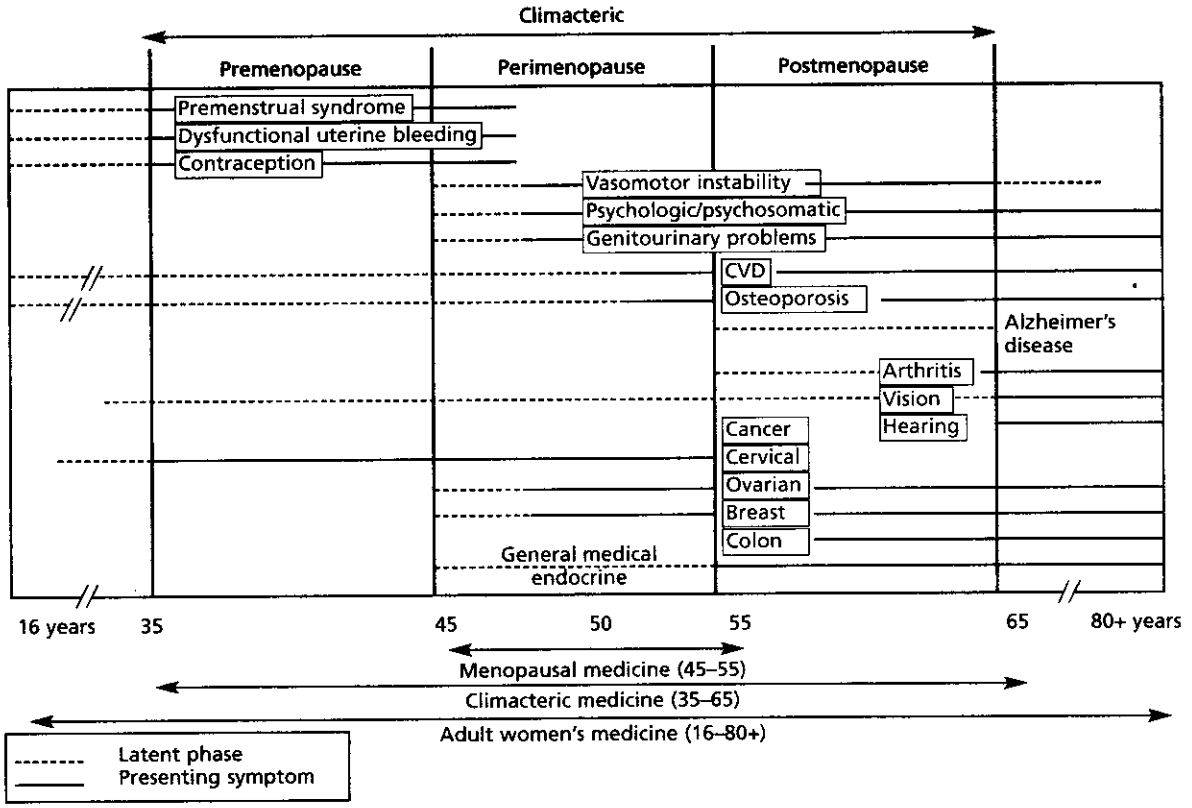

Figure 1: Women's health care needs according to life stage.

estrogen therapy needs to be based on the initial indication for therapy and gradually reduced over time.

2. Prescribe the lowest effective dose to meet the specific need of the individual for estrogen therapy. Re-evaluate annually and continue with estrogen therapy as long as the indication is still relevant for estrogen therapy and the benefit justifies any estrogen therapy-related risk.
3. Non-response to an appropriate dose of oral estrogen therapy may be influenced by the route of administration. Prior to increasing the estrogen dose, change the route of administration or add androgen to reduce SHBG.
4. Systemic blood levels of estradiol do not reflect the target tissue's concentration of estrogen. Thus, clinical response is a more reliable indicator of the efficacy of treatment.
5. There needs to be an indication for estrogen therapy. There is no one menopause, nor is there one hormone therapy nor dose of hormone therapy.

Pathogenesis of hormone-dependent conditions

The pathogenesis of hormone-relevant symptoms and conditions predates the menopause (*Figure* 2). For example:

1. Approximately 20% of premenopausal women have typical estrogen therapy-responsive vasomotor symptoms while still menstruating regularly. These symptoms typically occur in the late luteal and menstrual phase of the menstrual cycle and are due to a relative lack of estrogen [8]. These vasomotor symptoms respond well to low-dose transdermal estrogen.
2. Atheromatous changes are evident in young children. Most recently postmenopausal Caucasian women have evidence of coronary artery atherogenic (CAD) changes [1].

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3. Peak bone mass, the most significant risk factor for osteoporosis, occurs at about 30 years of age, and is followed by a slow decline in cancellous (and to a lesser extent cortical) bone in all women. This modestly accelerated state of bone resorption is further exaggerated during the 5–8 years following the menopause, and the decline in endogenous estrogen synthesis [9].

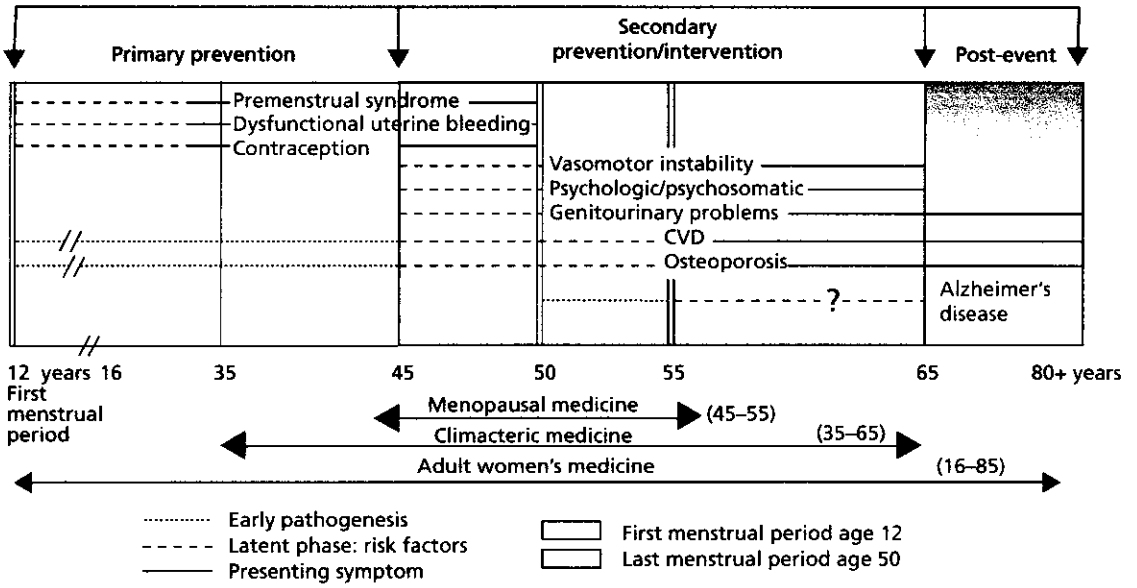

Figure 2: *The climacteric and menopause: the 'window of therapeutic opportunity' for hormone therapy.*

4. The onset of neurological changes associated with Alzheimer's disease is unclear, but clinically this condition is also antedated by a precondition: mild cognitive impairment [10].
5. The main concern of women on hormone therapy, or considering hormone therapy, is breast cancer. This disease – as is the case with CVD – is both complex and heterogeneic. Early-onset (<50 years) breast cancer is strongly related to high penetrance but low prevalence genes (mutated *BRCA1* and *BRCA2*); while the more common hormone-dependent breast cancers are associated with lower penetrance but more prevalent genes involving estrogen synthesis and metabolism [11]. Optimal maturation of the mammary epithelium and the stroma (the site of aromatization of androgen to estrogen) occurs premenopausally. Differentiated tissues develop a protective 'genetic fingerprint' that is maintained postmenopausally, thereby lessening the risk of breast cancer [12].

Hormone replacement, replenishment and maintenance

Estrogen and androgen receptors are present in all tissues, and premenopausally appear to mediate the physiological needs and functioning of relevant organs such as bone and the coronary artery endothelium. Premature ovarian failure or premenopausal oophorectomy removes this protective effect. Failure to replace or restore bioavailable and physiological amounts of estrogen in these women will result in the increased risk of, for example, osteoporosis or atherogenic CVD. This is not necessarily true for natural menopausal women, the majority of whom do not develop osteoporosis or CVD. Hence, there is a need to differentiate between hormone replacement therapy, hormone replenishment and hormone maintenance therapy (*Table I*).

Hormone replacement therapy refers to the replication of the physiological hormonal milieu of younger menopausal women (<50 years); hormone replenishment therapy refers to the pharmacological prescription of estrogen-progestogen in order to improve quality of life and to maintain tissue integrity and health (age 50–65 years); hormone maintenance therapy refers to the continuation of previously prescribed and well-tolerated hormone therapy. This approach predicates the clear definition of the goal of therapy and the need to distinguish between the primary and secondary prevention of conditions such as CVD. Early interventions in animal and human studies have shown that plaque formation can be stabilized and in some instances reduced by appropriately timed hormone therapy [1].

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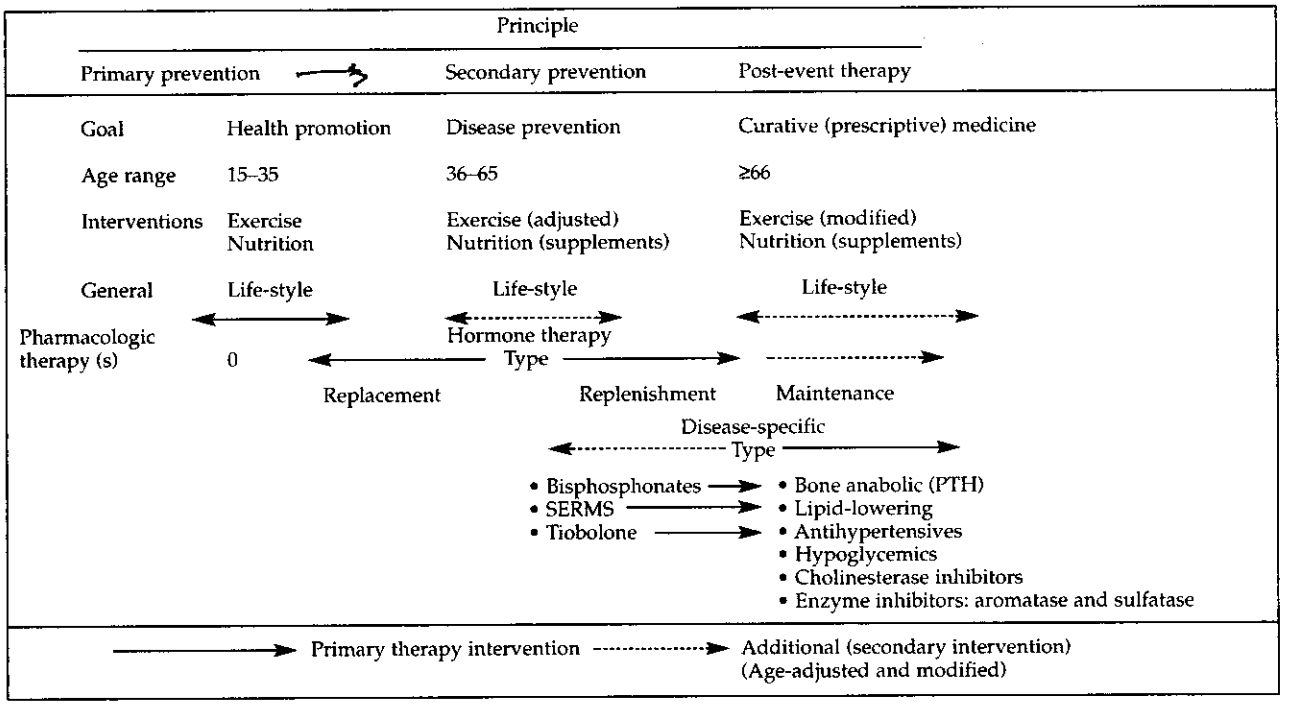
This is mediated by the favourable action of estrogen on lipid and lipoprotein metabolism, insulin resistance and blood pressure [13]. It has also been clearly established that oral estrogen increases the hepatic synthesis of cytokines and inflammatory agents such as the matrix metalloproteinases (MMP-9) [14]. Therefore susceptible fatty soft-core plaques with fragile fibrin cap-

Table 1: Pharmacology during the menopausal transition: applied clinical principles, the TACIT approach.



sules may be ruptured, creating a nidus for platelet aggregation, fibrin deposition and formation of an obstructing blood clot [15]. The risk of this occurring is very low when measured in absolute terms. These events are more likely to occur in women who have a pretreatment abnormality in the synthesis of the inflammatory cytokines, or who are hypersensitive to oral hormone replacement therapy and respond, for example, with excessive high-density lipoprotein (HDL) cholesterol synthesis [16]. In short, present or past significant CVD does not preclude the use of estrogen for estrogen-relevant symptoms, but it is contraindicated as a treatment for CVD.

Clinical application

1. The majority of menopausal women report symptomatically significant hot flushes, but the frequency and severity differ. Both the dose and duration of hormone therapy needed to relieve these symptoms vary. Approximately 4–8 weeks of estrogen therapy are required before significant relief is noted; hot flushes persist for 15 or more years in 20% of women [8].
2. Urogenital ageing and its associated conditions, including urethral and bladder dysfunction, are an inevitable consequence of ageing but may also be present in the early perimenopause. Routine annual testing of the pH of the lateral vaginal wall is recommended. Values greater than 4.5 are indicative of urogenital estrogen deficiency. Treatment is with local estrogen therapy.
3. Maintenance of the microarchitectural integrity of bone is essential for the primary prevention of osteoporosis. Treatment subsequent to a fragility fracture may prevent subsequent fractures (secondary prevention). Hormone therapy needs to be prescribed early and on a long-term basis for osteoporosis prevention and the dose gradually titrated downwards over time. Lower doses of estrogen therapy are effective in maintaining bone mineral density in older postmenopausal women. Monitoring with dual-energy x-ray absorptiometry and, in the author's opinion, with bone markers (urine calcium-creatinine ratio, urine collagen crosslink excretion, osteocalcin- or bone-specific alkaline phosphatase) is the only objective method of quantifying the efficacy of the prescribed therapy. Meticulous attention to bone mineral density testing technique and the timing and collection of blood and urine for bone marker assessment are central to the reliability of these technologies.
4. A fasting blood profile that measures glucose, cholesterol, triglycerides and HDL cholesterol will differentiate healthy women at low-risk of CVD from those with latent or overt (but asymptomatic) disease. The result will dictate the therapeutic approach: women with pretreatment low HDL cholesterol will benefit most from oral estrogen therapy; the presence of hypertriglyceridaemia is best treated with transdermal estrogen therapy; low-dose estrogen therapy (oral or transdermal) increases insulin sensitivity while high-dose estrogen therapy may increase insulin resistance. Improvement in these parameters (a hepatic effect) in women with significant established CVD is not an indication of a decrease in intimal disease but may be correlated with reduced progression of CVD [18]. Women with known or suspected significant

atheromatous disease should have C-reactive protein and possibly MMP-9 blood levels measured prior to estrogen therapy.

5. Estrogen has known neuronal functions that provide brain protection and the ability to correct certain aspects of neuronal dysfunction. Timing of estrogen therapy may be critical to the CNS benefit of appropriately prescribed hormone therapy, including the type and route of estrogen therapy [19]. Cognitive decline in ageing women is related to the level of bioavailable estrogen [20], as is improvement in visual memory and vigilance in non-demented healthy menopausal women on estrogen therapy. A number of questionnaires and validated tests are available for the early screening and identification of cognitive decline.
6. Excess local breast tissue estradiol synthesis has been correlated with both an increase in mammographic breast density and breast cancer [21]. High sensitivity breast estradiol blood values above 10–15 pg/ml are additional indicators of an increased risk of breast cancer [22]. Women with pretreatment dense breasts need to be carefully assessed and consideration given to treatment with tissue-specific hormones such as tibolone or a selective estrogen receptor modulator (SERM) such as raloxifene [22]. Hormone therapy, if indicated, should be limited to the lowest effective dose. Transdermal estrogen therapy is least likely to increase levels of estrone and estrone sulfate, both of which may serve as substrates for the local breast tissue synthesis of estradiol.

A rational approach to hormone therapy: individualization

The standards of clinical practice are increasingly governed by the outcomes of randomized, placebo-controlled, clinical trials. This approach presupposes that the disease or condition under investigation, the subjects concerned and the treatment being evaluated are all equal or similar. This is clearly not the case as far as the menopause is concerned: as noted previously, although the menopausal transition is generic to all women, the biological changes that determine clinical behaviour and the postmenopausal hormone milieu are varied and individualized. So too are the pharmacodynamic and pharmacokinetic responses of women to both the same and different forms, routes and dosages of hormone therapy. Age-related variables further confound the issue and need to be factored into the rationalization of hormone deficiency (or its replacement), with the causation (or prevention) of a given disease.

Understanding the pathogenesis of related and relevant diseases does place into context the potential attributable benefit or risk of hormone therapy. The separation of true primary prevention from secondary intervention is possible and so allows for the identification of a 'window of therapeutic opportunity' for hormone therapy. This clinical approach is predicated by the selective and judicious use of technology that can define the health status of a given woman at a given point in time. Further, it is possible to quantify the presence and relevance of a given condition and the need for hormone therapy. Tailoring hormone therapy to the needs of the individual is possible, but it involves time and technology, both of which are costly and may not be available for routine care. The applied message is, however, clear: oversimplification of the menopause and postmenopause and the use of standardized and uniform dosages of hormone therapy, or the empiric restriction of hormone therapy to an arbitrary period of time, are bound to result in many patients being inappropriately or over/under-treated. Clinical practice differs from clinical trials in one important additional respect: consideration of the dynamic changes that occur with time and adapting treatment according to need. Depending on clinical circumstances, it is entirely appropriate to treat symptomatic menopausal women with hormone therapy for some years and then switch to SERMs, bisphosphonates or statins based on emerging clinical indication(s). This *t*ime-*a*djusted *c*linically *i*ndicated *t*reatment (TACIT) approach is summarized in *Table I*. It is equally appropriate to maintain a woman on long-term hormone therapy (>5 years) as long as the need for it remains and there are no significant adverse effects. The clinical needs and treatment of all menopausal women should be re-evaluated annually.

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